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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,874	PECKER ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of the specification, claims 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66 and 68-70 in the Paper of 10/1/2003, is acknowledged.

Claims 14-70 are still at issue and are present for examination.

Applicants' arguments filed on 10/1/2003 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

The disclosure is objected to because of the following informalities:

Applicants amendment of the specification at page 54, lines 14-16 to recite "Insect cells are known to produce proteins free of PAI1 (type1 plasminogen activator inhibitor)." is objected to because this recitation is not supported by the original specification and is therefore considered new matter.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previous rejection of claims 68-70 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is hereby withdrawn based on applicants amendments of the claims. It is noted that this withdrawn rejection is that previously made against claims 68-70 as a group, not the previous rejection of claims 14-63 and 68 which is maintained below.

Claims 14-63 and 68 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action. In response to this rejection applicants continue to traverse the rejection on the following basis.

Previously it was noted that applicants amendment to claims 14-63 which recite "the preparation being free of non-heparanase polypeptides encoded by human nucleic acid sequences" (claims 14, 15, 24, 34, 35, 44, 45, 54, 55 and 68), "... said isolated protein being substantially devoid of glycosilation..." (claims 16, 17, 26, 27, 36, 37, 46, 47, 56 and 57), "...the preparation being substantially free of a CXC chemokine or PAI1" (claims 18, 19, 28, 29, 38, 39, 48, 49, 58 and 59), "...said isolated protein characterized by insect cell derived sugar prosthetic groups..." (claims 20, 21, 30, 31, 40, 41, 50, 51

60 and 61), or "...said isolated protein characterized by non-human cell derived sugar prosthetic groups..." (claims 22, 23, 32, 33, 42, 43, 52, 53, 62, and 63), are not supported by the original disclosure and therefore considered new matter.

Applicants continue to submit that all of the previous limitations have clear support in the specification and as an example applicants repeat their expanded analysis of why the specification supports the limitation that recites "the preparation being free of non-heparanase polypeptides encoded by human nucleic acid sequences". Applicants argument is still not found persuasive, because using such an analysis does not justify support for the above limitations. Just because the recited limitation is a property of a recombinant protein produced by a particular method, does not support a claim to such a property. Applicants did not contemplate the claimed limitation/ subgenus at the time of filing, and hence the inclusion the above limitations limiting the claims to the above referred to sub-genuses is considered new matter.

Similar arguments made for the remaining limitations would also be found non-persuasive for similar reasons. In response to applicants comments that the examiner did not specifically point out why the above references were insufficient to show that one of skill in the art would easily recognize and appreciate these claimed properties from the specification as it now stands, as stated previously and repeated above, applicants did not contemplate the claimed limitation/subgenuses at the time of filing, and hence the inclusion the above limitations limiting the claims to the above referred to sub-genuses is considered new matter. Each of the specific limitations referred to above constitute a specific subgenus, that while the species of which are encompassed

by the originally claimed genus, these subgenuses of which each of the these limitations refer to are not supported by the original specification.

Claims 14-33, 34-43, 44-65 and 66-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein or preparation comprising said protein having the amino acid sequence of SEQ ID NO: 10, said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, does not reasonably provide enablement for any protein or preparation comprising said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, regardless of whether said protein is about 50 or about 65 kDa, has a pair of glutamic acids participating in its active site, or capable of eliciting anti-heparanase antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was made in the previous office action for claims 14-70. In response to this rejection applicants traverse the rejection on the following basis. Applicants state that their amendment drawn to polypeptides having a mere 60% homology to SEQ ID NO: 10 or a portion thereof (referring to claims 68-70), clearly overcomes the rejections by the examiner, as a clear structural relationship is drawn between the species disclosed and the claimed polypeptides. While such an amendment may be sufficient to overcome the basis of the previous 112 first paragraph rejection based on written description, such an amendment is insufficient to overcome

the previous 112 first paragraph rejection based on a lack of enablement for the reasons previously stated. Applicants are reminded that such a limitation previously occurred for a number of the other claims also included in the set of those claims currently rejected under this statue.

Applicants then further traverse the rejection, as well as the more general rejection of lack of enablement (???) and also the rejection for lack of written description on the following grounds:

Applicants assertion that nucleic acids and proteins are chemical entities and as such are entitled to at least similar consideration for enablement and written description requirement issues is acknowledged and agreed with. Applicants submit that the previous written description and enablement requirements of the US Patent and Trademark Office as stated in the rejections by the Examiner, do not appear to take any applicants comments related to the above into consideration. As an example applicants refer to the statement by the examiner which recites, "the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable" and applicants note that a similar statement could be made for any type of chemical entity. Applicants then submit that the examiner has imposed a new requirement on proteins which has not been previously imposed on other types of chemical entities. This submission and applicants arguments based upon such is not found persuasive, as the above referred to statement was merely made to show the unpredictability of the art (See In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) factor (7) the predictability or unpredictability of the art). This statement was

further supported by a reference supporting such a position (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). Thus as previously stated given such unpredictability in the art, applicants lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the heparanase catalytic activity claimed, it would require undue experimentation for one skilled in the art to arrive at the majority of those proteins of the claimed genus having the claimed heparanase catalytic activity.

Applicants further argue that the position and understanding of those scientists in the technological field concerning homology is at odds with the examiner's assertion of undue experimentation with regard to homology as determined from protein and/or DNA/RNA sequences. As applicants assert, many genes have been identified according to sequence similarity, however the identification of specific genes based upon sequence homologies does not necessarily enable one of skill in the art to predict those residues which may be altered without affecting the function of the encoded proteins. Applicants attention is again drawn to the above referred to reference supporting such a position. Applicants argue that mere degree of homology is sufficient to establish a protein as a heparanase, and while in the case of extremely high percent homology this may be true, in the absence of such homology, additional characteristics are necessary to enable such a broad genus such as those previously stated (i.e. (A) regions of the protein structure which may be modified without effecting heparanase catalytic activity; (B) the general tolerance of heparanases to modification and extent of

such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a heparanase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful).

Applicants further argue that the examiner's rejections are contrary to Markush practice and that the present claims follow Markush practice. Applicants submit that it is not possible to predict with absolute accuracy the function and effect of molecules routinely covered by Markush groups such as a regular drug for example, yet broad claim coverage is allowed for the entire group of such molecules on the basis of highly limited examples. Applicants submit that the currently structured claims of the present application deserve the same consideration as though they were written in the form of Markush groups, because in fact a claim structure on the basis of homology to a nucleic acid or amino acid sequence is functionally equivalent to a Markush group. Regardless of applicants above assertions applicants arguments as they apply to the current 112 first paragraph rejections are not found persuasive.

Applicants further argue that the present claims do not involve undue experimintation based on applicants examination of the *Wands* factors with regard to the present claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Applicants comments with respect to each of the individual *Wands* factors are noted, as applicants submit that : the present application provides a simple routine test in order to determine if a particular protein belongs to the claimed invention and that preparation of such proteins is simple; applicants provide a great deal of direction and guidance as to how to select a protein having heparanase activity; and applicants provide sufficient working examples. Applicants comments with respect to the nature of the invention, state of the art and skill of those in the art, predictability of the art as well as the breadth of the claims are acknowledged.

Applicants argument is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. as well as methods of identifying such variants are well known to the skilled artisan producing variants as claimed by applicants (i.e., having heparanase activity) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparanase catalytic activity; (B) the general tolerance of heparanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a heparanase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any heparanase having a mere 60% homology to SEQ ID NO: 10. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 64, 65, 66, 67, 69 and 70 remain rejected under 35 U.S.C. 102(b) as being anticipated by Fuks et al. (U.S. Patent No. 5,362,641).

The rejection was originally stated in the office action, 10/21/2003, and maintained in the previous office action of 7/1/2003.

Applicants continue to traverse this rejection on the following basis .

Applicants continue to traverse this rejection on the basis that the "the antibody of Fuks cannot anticipate claims 64 and 65, as the antibody of claims 64 and 65 recognizes heparanase, while that of Fuks does not. As previously stated, this argument is not found persuasive because the rejected claims are drawn to a protein not an antibody and irrespective of any antibody prepared and isolated by Fuks, the protein of Fuks is capable of eliciting an anti-heparanase antibody. Just because Fuks reportedly were unsuccessful in generating an antibody does not change this inherent limitation of the protein taught by Fuks.

In response to the above applicants submit that the recitation of an antibody is important for characterization of the protein, and therefore the preparation of Fuks et al. fails in this respect to elicit an anti-heparanase antibody. This argument continues to not be found persuasive because regardless of applicants argument the rejected claims recite "said protein being capable of eliciting an anti-heparanase antibody" and this is an inherent property of the protein taught by Fuks et al. It is capable of eliciting an anti-heparanase antibody.

With respect to claims 66-70, applicants argue that Fuks et al. fail to teach or suggest any of the important limitations of these claims, such as the sequence of the taught heparanase. In response applicants are reminded that the heparanase taught by Fuks et al. inherently has an amino acid sequence which meets the limitations of the rejected claims, and thus Fuks et al. need not teach this specific sequence in order to anticipate the claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
12/09/2003